PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61M 16/00, A61N 1/36

A1

(11) International Publication Number: **WO 00/01438**

(43) International Publication Date: 13 January 2000 (13.01.00)

(21) International Application Number: PCT/IB99/01345

(22) International Filing Date: 5 July 1999 (05.07.99)

(30) Priority Data:
98/08639 6 July 1998 (06.07.98) FR

(71) Applicant *(for all designated States except US)*: ELA MEDICAL S.A. [FR/FR]; 98, rue Maurice Arnoux, F–92541 Montrouge (FR).

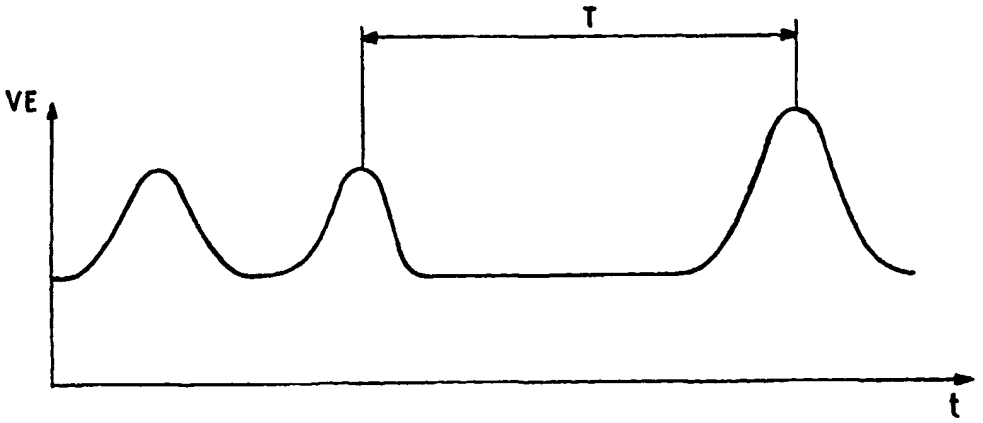
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BONNET, Jean–Luc [FR/FR]; 44, place Jules Ferry, F–92120 Montrouge (FR).

(74) Agent: DUPUIS–LATOUR, Dominique; Cabinet Bardehle, Pagenberg & Partner, 14, boulevard Malesherbes, F–75008 Paris (FR).

(81) Designated States: JP, US.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AN ACTIVE IMPLANTABLE MEDICAL DEVICE FOR TREATING SLEEP APNEA SYNDROME BY ELECTROSTIMULATION



(57) Abstract

An active implantable medical device for electrostimulation in response to a determined sleep apnea syndrome, particularly a pacemaker. This device measures the respiratory activity of the patient, using for example, a minute ventilation sensor and/or a blood oxygen saturation sensor, and analyzes the sensor signal, to determine occurrence of an apnea according to the signal delivered by the sensor. The device also delivers an increase cardiac pacing rate in the event of detection of an apnea. The device also can deliver a neurological and/or cardiac stimulation so as to apply selectively to the patient an electric stimulus. The device also determines the patient's state of activity, according to predetermined criteria, such that the increased pacing rate is provided only during a sleep phase and otherwise inhibited. The analysis can in particular detect an occurrence of successive apnea during a phase of sleep and determine the occurrence of a sleep apnea syndrome when the number of apnea events detected during a given period of time exceeds a predetermined threshold.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Title: AN ACTIVE IMPLANTABLE MEDICAL DEVICE FOR TREATING SLEEP APNEA SYNDROME BY ELECTROSTIMULATION

Field Of The Invention

The present invention relates to the diagnosis of the syndrome of sleep apnea and more particularly, cardiac pacemakers able to detect sleep apnea and respond to the detection with electrostimulation.

Background Of The Invention

The syndrome of sleep apnea ("SAS"), more precisely the syndrome of obstructive and non central sleep apnea ("SOAS") is an affliction having generally as its origin an obstruction of the respiratory tracts. It is likely to involve a certain number of disorders such as painful and/or insufficient breathing, an abnormal heartbeat, and hypertension. Various treatments of SAS have been proposed, including treatments involving surgery, medication, and maintenance of a positive pressure in the respiratory tract by means of a facial mask worn during sleep.

One technique, as discussed in EP-A-0 702 979 (to Medtronic) proposes to treat SAS by electrostimulation. This document describes an implanted pulse generator, controlled by a sensor, which may be a dynamic pressure sensor or a sensor of intrathoracic impedance, making it possible to follow (monitor) the patient's respiration rate and thus to detect the occurrence of an apnea. When an apnea is detected, the generator delivers a salvo (sequence) of pulses to a stimulation electrode implanted in the muscles controlling the patient's airway. This technique is not, however, in practice, completely satisfactory. This is because the stimulation which is systematically started in the event of an increase in the intratracheal pressure, whatever the cause of this increase in pressure, and whether it is due to an SAS or not, will include inappropriate stimulations.

Pacemakers having a cardiac stimulation or pacing rate which is responsive to a detected physiological or physical parameter of the patient are known. Generally, as the measured parameter increases, it reflects an increasing level of activity of the patient (e.g., exercise), and the stimulation frequency increases so that the pacing rate is controlled to

simulate the action of a normal heart. Once such style of pacing device measures the patient's so-called minute ventilation (minute volume) based on a transthoracic of intrathoracic impedance measurement. An earlier style of such a pacing device measured the respiration rate, but this parameter is generally believed to be less useful as a physiological parameter because it does not represent the patient's metabolic demand (also referred to as the cardiac output requirements) during phases of increased patient activity.

Objects and Summary of the Invention

It is, therefore, an object of the invention to propose a device for the treatment of SAS by electrostimulation.

Broadly speaking, the present invention concerns analyzing the metabolic and functional state of the patient, for applying, selectively, a stimulation for the treatment of SAS only during the phases of patient activity where an SAS is really likely to appear, and otherwise inhibiting any SAS stimulation.

One aspect of the invention is directed to a device which is an active implantable medical pacemaker device allowing for the treatment by increased cardiac electrostimulation of the sleep apnea syndrome in a patient, i.e., including: means for measuring the respiratory activity of the patient; means for analyzing and determining an occurrence of an apnea in response to the measured respiratory signal; and means for delivering an SAS stimulation, controlled by the analyzing means, so as to apply selectively to the patient an increased cardiac stimulation rate in the event of a detection of an apnea. The SAS stimulation means is preferably a circuit which delivers SAS stimulation by increasing cardiac stimulation rate, and the respiratory activity measurement means may be a circuit which includes a minute ventilation sensor or a sensor which detects the oxygen saturation of the blood.

According to a preferred embodiment of the present invention, this device also includes means for determining a state of activity of the patient, this state being likely to take, according to predetermined criteria, a value representative of a state of sleep (also referred to as a rest phase) of the patient, such that the SAS stimulation means is triggerable only during a determined phase of sleep and otherwise is inhibited.

According to other various advantageous characteristics of the invention, the analyzing means detects an occurrence of a syndrome of sleep apnea when the number of apnea occurrences detected during a given period of time exceeds a predetermined threshold. In another embodiment, the determining means optionally determines a state of activity by analyzing the signal delivered by the means for measuring the respiratory activity of the patient, and/or by a separate auxiliary measurement means.

Brief Description Of The Drawings

Other features, characteristics and advantages of the present invention will appear to a person of ordinary skill in the art in view of the following description, which is made with reference to the drawings annexed, in which Figs. 1 and 2 illustrate a signal representative of the respiration rate of the patient, in the absence of disorder and at the time of occurrence of an apnea respectively.

Detailed Description Of The Invention

With reference to the drawing, an evolution of the respiration rate of a patient during sleep is shown. It is represented by the evolution over the course of time of the minute ventilation signal. (signal VE, also called signal MV), which is a parameter obtained by a measurement of intrathoracic impedance that is predominantly physiological in nature. Although the minute ventilation signal is generally easy to implement for monitoring the respiration rate of the patient, other signals coming from other types of sensors can be used in the alternative or in addition to the minute ventilation sensor, for example, a sensor measuring blood oxygen saturation.

The measurement of the minute ventilation parameters is in itself well-known. The measurement is obtained between two electrodes placed in the rib cage, or if the implanted device is a pacemaker, between an electrode (for example, a stimulation electrode) and the case of the implanted medical device. The impedance is then measured in response to an injection of a constant current of a few hundreds of microamperes, at a frequency of a few hertz, typically 8 Hz. This technique is described, for example, by J.L. Bonnet et al., "Measurement of Minute-Ventilation with Different DDDR Pacemaker Electrode Configurations", PACE, Vol. 21, 98, Part 1, and it is implemented in the commercial rate responsive pacemaker devices sold under the trademark Chorus RM 7034, by ELA Médical, Montrouge, France.

One can determine, starting from this signal, a respiratory period T (Fig. 1) which is defined as the time separating two detected impedance peaks. The peaks correspond to the high impedance obtained at the time of the inspiration (lungs being filled with air), and the decrease of the impedance corresponds to an expiratory phase.

Referring to Fig. 2, a waveform representative of a minute ventilation signal recorded among patients suffering from sleep apnea is shown. These patients have normal expiratory phases, because the pulmonary pressure is sufficient to overcome the obstruction. On the other hand, the inspiration is abnormal because the lungs cannot fill with air.

One then can observe, as illustrated in Fig. 2, an important lengthening of the respiratory period T after an expiration.

The first stage concerns diagnosing a sleep apnea occurrence. An apnea is classically defined as a respiratory pause of a duration that is greater than ten seconds, a phenomenon which is relatively easy to detect by monitoring minute ventilation. Moreover, this pause must occur during a sleep phase of the patient, because an apnea occurring while the patient is in an awake state cannot be caused by an SAS.

To respect the latter criterion, the invention proposes to discriminate between the sleep phase and the awake phase of the patient, and to apply an SAS therapy only during the sleep phase. Any treatment of an apnea which is detected during an awake phase is inhibited because, in this case, the apparent apnea normally is not pathological.

The sleep period can be diagnosed, of course, automatically, either starting from the signal delivered by the sensor monitoring the respiration activity of the patient, or by a separate sensor, for example, an activity sensor which measures a parameter which is predominantly physical such as acceleration as may be measured by an internal sensor located within the case.

EP-A-0 719 568 and its counterpart United States Patent No. 5,622,428 commonly owned by ELA Médical describe in particular determining a "criterion of activity of a sensor", making it possible to make a distinction between the phases of rest (night or diurnal), and activity of the patient, in particular for contrast with a minute ventilation sensor. U.S. Patent No. 5,622,428 is incorporated herein by reference in its entirety.

The EP-A-0 750 920 and its counterpart United States Patent No. 5,722,996 and EP-A-0 770 407 and its counterpart United States Patent 5,766,228 both commonly assigned to ELA Médical, describe medical devices using combined information of a physiological sensor and a physical sensor, in particular a minute ventilation sensor and an accelerometer, to determine a state of a activity or a state of rest of the patient. U.S. Patent No. 5,722,996 and 5,766,228 are incorporated herein by reference in their entirety.

Thus, having diagnosed an apnea, and having confirmed that this apnea is a sleep apnea, one then can carry out a calculation of an index of apnea. In this regard, when the apnea index exceeds a predetermined threshold, for example, more than ten apnea occurrences per hour (this threshold number can, of course, be programmable to be suitable for the particular patient), the presence of an SAS is determined. As soon as an SAS is diagnosed, an electric stimulation is then applied to the patient to compensate for the harmful effects of the SAS.

The electric stimulation can be a muscular stimulation (as described, for example, in the EP-A-0 702979 mentioned above or a neurological stimulation, to cause the immediate opening of the esophagus in order to allow inspiration. In the latter case, a neurological stimulation preferably will be applied only during the inspiratory phases of the patient's breathing cycle so as not to disturb the expiratory phase.

One also can envisage an embodiment whereby a stimulation is delivered only if the inspiratory period exceeds a preset value, for example, six seconds.

Further, in the preferred embodiment, the electric stimulation is a cardiac stimulation, for example, to accelerate the heart rate (frequency) of the myocardium, to compensate for the effects of the SAS. Such a cardiac stimulation will be applied to as soon as an SAS is diagnosed, by increasing the stimulation frequency by a few beats per minute (typically +10 bpm), compared to the natural sinusal rate of the patient. The stimulation at the higher rate is applied for a given period of time, for example, sixty seconds and afterwards the device reverts to the former mode of operation, e.g., the lower stimulation frequency. It also should be understood that the increased cardiac stimulation can be applied together with a muscular and/or a neurological stimulation in response to a determined SAS.

One skilled in the art should understand that the invention is not limited to the disclosed embodiments, which are presented for purposes of illustration and not of limitation.

I claim:

1. A cardiac stimulation device for treating the syndrome of the sleep apnea of a patient by electrostimulation comprising:

means for measuring the respiratory activity of the patient having an output signal representative of the patient's respiratory activity;

means for analyzing the patient's respiratory activity according to the output signal from the respiratory measuring means to determine an occurrence of an apnea;

means for determining a cardiac rate of the patient, including a second rate in the absence of a determined apnea;

means for stimulation, controlled by the analyzing means, to apply selectively to the patient cardiac stimuli at a first rate in the event of a detection of an apnea, said first rate being higher than the second rate;

means for determining a state of activity of the patient, said state being selected, according to predetermined criteria, from among a first value representative of a sleep state of the patient and a second value representative of an awake state of the patient;

wherein the stimulation means is applying to the patient cardiac stimuli at the first cardiac rate only during a determined sleep phase.

2. The device of claim 1 in which the stimulation means stimulates in response to being triggered at the first rate, wherein the first rate is at least 10 beats higher than the second rate.

3. The device of claim 1, in which the analyzing means detects an occurrence of successive apnea during a sleep phase and determines an occurrence of a syndrome of apnea of the sleep when the number of apnea detected during a given period of time exceeds a predetermined threshold.

4. The device of claim 1, in which the means of determination of a state of activity further comprises analyzing the output signal from said measuring means.

5. The device of claim 1, further comprising an auxiliary measuring means for measuring a state of activity of the patient; wherein the means for determining the state of activity further comprises means for analyzing the output signal from the auxiliary measuring means, said auxiliary measuring means output signal being distinct from said means for measuring of the respiratory activity of the patient.

6. The device of claim 1, further comprising an auxiliary means for measuring a state of activity of the patient, wherein said auxiliary measuring means further comprises an accelerometer.

7. The device of claim 1, wherein the means for measuring the respiratory activity of the patient further comprises a minute ventilation sensor.

8. The device of claim 1, wherein the means for measuring the respiratory activity of the patient further comprises a sensor of oxygen saturation of blood.

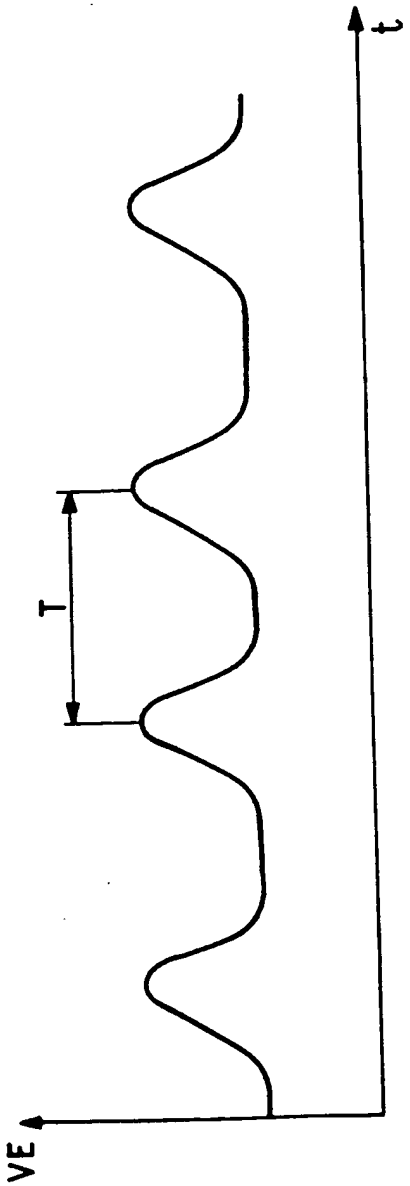


FIG_1

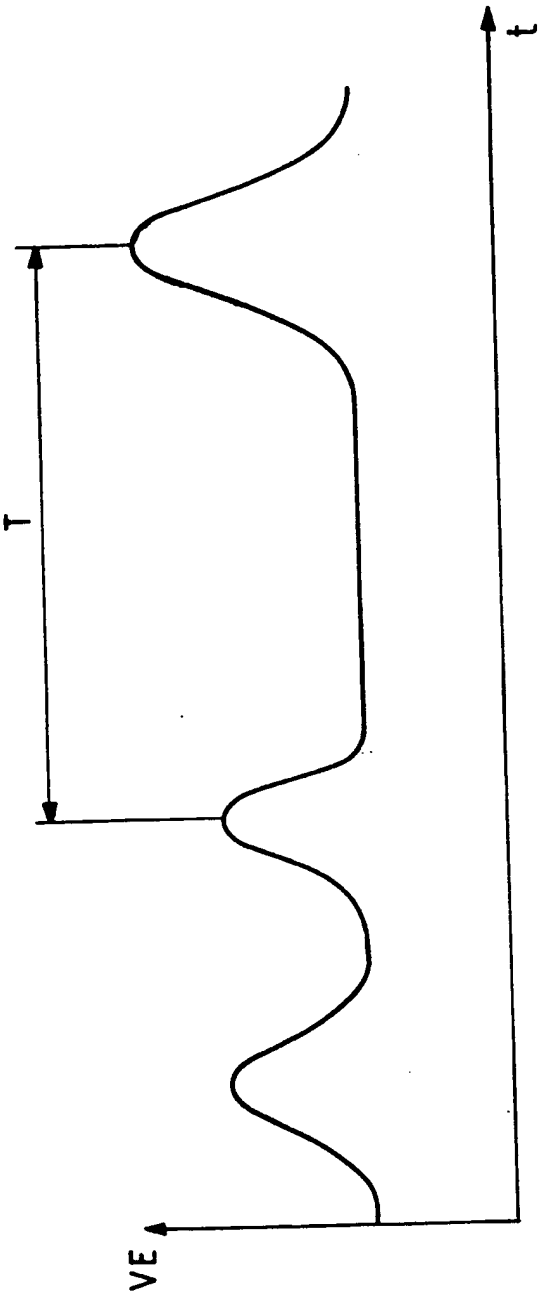


FIG_2

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/IB 99/01345

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M16/00 A61N1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 485 851 A (ERICKSON DONALD J) 23 January 1996 (1996-01-23) cited in the application abstract; figure 23 column 5, line 22 -column 6, line 45 column 11, line 34 -column 12, line 19 column 14, line 19 -column 16, line 43 ---	1-8
Y	US 5 713 933 A (GREENINGER DANIEL J ET AL) 3 February 1998 (1998-02-03) abstract; figures column 1, line 57 -column 2, line 9 column 5, line 64 -column 6, line 16 & WO 96 16696 A (MEDTRONIC INC) 6 June 1996 (1996-06-06) ---	1-8
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1999	10/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Zeinstra, H

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter- onal Application No
PCT/IB 99/01345

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate. of the relevant passages	Relevant to claim No.
A	US 5 024 222 A (THACKER JAMES R) 18 June 1991 (1991-06-18) column 3, line 5 - line 16; figures 5,6	1-8
A	EP 0 750 920 A (ELA MEDICAL SA) 2 January 1997 (1997-01-02) cited in the application abstract; figures column 1, line 19 - line 25 column 4, line 21 -column 5, line 37	1,6,7
A	EP 0 770 407 A (ELA MEDICAL SA) 2 May 1997 (1997-05-02) cited in the application abstract; figure 1 page 2, line 6 - line 13 page 3, line 44 -page 4, line 19	1,6,7
A	WO 92 03983 A (EDENTEC ;SHANNON JOHN L JR (US); BOWMAN BRUCE R (US)) 19 March 1992 (1992-03-19) abstract; figure 1 page 7, line 1 -page 8, line 15	1
A	WO 84 02080 A (TRITEC IND INC) 7 June 1984 (1984-06-07) abstract; figures 8A-8C page 31, line 11 - line 19 page 38, line 1 - line 12	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 99/01345

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5485851	A	23-01-1996	NONE		
US 5713933	A	03-02-1998	AU	4156696 A	19-06-1996
			CA	2206404 A	06-06-1996
			EP	0794814 A	17-09-1997
			JP	10513368 T	22-12-1998
			WO	9616696 A	06-06-1996
			US	5902325 A	11-05-1999
			US	5843137 A	01-12-1998
US 5024222	A	18-06-1991	AU	622097 B	26-03-1992
			AU	7015491 A	22-08-1991
			DE	69119263 D	13-06-1996
			DE	69119263 T	19-09-1996
			EP	0443495 A	28-08-1991
			JP	1872827 C	26-09-1994
			JP	4218172 A	07-08-1992
			JP	5079347 B	02-11-1993
EP 0750920	A	02-01-1997	FR	2735985 A	03-01-1997
			US	5722996 A	03-03-1998
			JP	9164213 A	24-06-1997
EP 0770407	A	02-05-1997	FR	2739782 A	18-04-1997
			JP	9182806 A	15-07-1997
			US	5766228 A	16-06-1998
WO 9203983	A	19-03-1992	US	5123425 A	23-06-1992
			AU	8427891 A	30-03-1992
			US	5265624 A	30-11-1993
WO 8402080	A	07-06-1984	US	4462398 A	31-07-1984
			US	4506666 A	26-03-1985
			US	4461293 A	24-07-1984
			AT	79775 T	15-09-1992
			AU	601042 B	30-08-1990
			AU	1645088 A	11-08-1988
			AU	577775 B	06-10-1988
			AU	2332484 A	18-06-1984
			CA	1231416 A,C	12-01-1988
			DE	3382613 A	01-10-1992
			EP	0127675 A	12-12-1984
			HK	87693 A	03-09-1993
			US	4519387 A	28-05-1985
			US	4570631 A	18-02-1986